syrup odor), oasthouse urine disease (yeast-like, dried celery odor), two disorders that result in an odor of sweaty feet, the fish odor syndrome (odor of decaying fish), and the odor of rancid butter syndrome.

It is readily apparent that through the sense of smell an astute physician can diagnose some unusual disorders of metabolism and institute life-saving therapy while awaiting laboratory confirmation.

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Improved Survival of Patients with Acute Lymphoblastic Leukemia Receiving Early Central Nervous System Treatment

AS THE CHEMOTHERAPY of the hematologic manifestations of acute lymphoblastic leukemia has improved and resulted in longer survival, the incidence of central nervous system (CNS) leukemia has risen. Additionally, the appearance of leukemic cells in the CNS rather than in the peripheral blood or bone marrow as the first evidence of termination of complete remission has been reported in 30 to 60 percent of children. The presence of malignant cells in the CNS sanctuary protected from antileukemic drugs may be an important source of cells which later produce CNS symptoms and hematologic exacerbations. These statistics and hypothesis have formed the rationale for intensive early treatment and prophylaxis of the CNS and offer the hope that with eradication of this malignant cell reservoir, symptom-free survival will be prolonged further with cure a possibility.

The most successful methods of CNS treatment are (1) irradiation of the entire cranio-spinal axis with 2,400 radiation absorbed doses (RADS); (2) repeated administration of intrathecal methotrexate; or (3) a combination of cranial irradiation, 2,400 RADS, with intrathecal methotrexate. A decrease to 4.4 percent from 15 percent in the incidence of the CNS as the site of the first evidence of relapse has been achieved, and these treatment programs provide excellent evidence of long-term disease-free survival in at least 50 percent of patients. All children with acute lymphoblastic leukemia should receive CNS treatment early in the course of their disease as part of their total therapeutic program.

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Antiviral Agents and Their Use in Pediatrics

DRUGS THAT HAVE BEEN LICENSED as antiviral agents include thiosemicarbazone, idoxuridine and amantadine. The thiosemicarbazones are synthetic compounds that interfere with the assembly of virus particles. *In vitro* they are active against pox viruses (variola and vaccinia), and *in vivo* they have been found useful in preventing smallpox and treating vaccinia gangrenosum and eczema vaccinatum. Vomiting sometimes occurs with the use of these drugs.

Idoxuridine (IDU) is a synthetic compound that interferes with deoxyribonucleic acid (DNA) synthesis. It is active *in vitro* against certain DNA-containing viruses including herpes simplex (HSV), varicella-zoster (VZ), human cytomegalovirus (CMV), vaccinia, and adenoviruses.

These compounds are useful locally in herpes simplex keratitis and vaccinia keratitis. There is anecdotal evidence that parenterally these drugs may be useful in vaccinia, certain overwhelming VZ infections in immunosuppressed patients and certain cases of generalized HSV and CMV infections of the neonate. These compounds can cause gastrointestinal distress, bone marrow depression and skin lesions. Besides the fact that drug resistance develops during therapy, the drug is incorporated into the DNA molecule and may be carcinogenic.

Amantadine is a synthetic compound that interferes with the penetration of virus into cells. It is active *in vitro* against influenza A, parainfluenza, respiratory syncytial and rubella viruses. Although amantadine rarely has been used in patients with the congenital rubella syndrome, there is no firm evidence that its use was associated with significant long-range clinical improvement or with eradication of the virus. Its clinical usefulness has been in protecting humans against influenza A virus infection when administered before infec-

tion. Central nervous system manifestations have been observed with high doses.

Several compounds, although not licensed as antiviral agents, show antiviral activity *in vitro* and have been used *in vivo* with Food and Drug Administration approval. Cytosine arabinoside (ARA-C) is a synthetic compound that interferes with DNA synthesis. It is active *in vitro* against the herpesviruses (HSV, CMV, VZ). Evidence, although not well controlled, suggests that this compound is useful in certain cases of disseminated VZ or HSV infections in patients with immunosuppressive diseases and in certain CMV infections in children with renal homotransplants or malignancy. The only controlled study, using excessive amounts of ARA-C, does not confirm the usefulness of this drug but results may be related to the high dosage used. Cases of generalized HSV infections of the neonate and cytomegalic inclusion disease of infancy have been treated with ARA-C with variable results; this drug probably subdues but does not eradicate the viral infection. Toxicity is manifested by bone marrow depression, gastrointestinal distress, bleeding diathesis, liver dysfunction, rash, phlebitis, fever and hair loss. Adenine arabinoside (ARA-A) is a synthetic compound, similar to ARA-C, but apparently has less toxicity and produces a more prolonged antiviral effect. Clinically, ARA-A has been considered useful in certain mucocutaneous diseases caused by HSV, vaccinia and VZ as well as certain congenital CMV and severe HSV infections.

A controlled, multi-institutional study is needed to determine whether treatment with IDU, ARA-C or ARA-A is clinically effective. The present lack of clinically useful antiviral drugs is largely because agents that suppress viral replication also affect the metabolic activity of the uninfected cell.

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